1: Blood 2002 Feb 1;99(3):1038-43

The mechanism of tumor cell clearance by rituximab in vivo in patients with B-cell chronic lymphocytic leukemia: evidence of caspase activation and apoptosis induction.

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Rituximab is a chimeric monoclonal antibody directed at CD20 with significant activity in non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). A variety of pathways of tumor cytotoxicity different from cytotoxic chemotherapy have been proposed for this therapeutic antibody including antibody-dependent cellular cytotoxicity and complement-mediated cell lysis. This report describes that a proportion of patients with CLL receiving rituximab treatment have in vivo activation of caspase-9, caspase-3, and poly(ADP-ribose) polymerase (PARP) cleavage in blood leukemia cells immediately following infusion of rituximab. This suggests that apoptosis using a pathway similar to fludarabine and other chemotherapeutic agents is intricately involved in the blood elimination of tumor cells after rituximab treatment. Patients having caspase-3 activation and PARP cleavage in vivo had a significantly lower blood leukemia cell count after treatment as compared to those without caspase activation. Significant down-modulation of the antiapoptotic proteins XIAP and Mcl-1 was also noted, possibly explaining in part how rituximab sensitizes CLL cells to the cytotoxic effect of chemotherapy in vivo. These findings suggest that the therapeutic benefit of antibody-based therapy in vivo for patients with CLL depends in part on induction of apoptosis and provides another area of focus for studying mechanisms of antibody-resistance in neoplastic cells.

Publication Types:
- Clinical Trial
- Multicenter Study

PMID: 11807010 [PubMed - indexed for MEDLINE]

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online

Elevated levels of biologically active soluble CD40 ligand in the serum of patients with chronic lymphocytic leukaemia.

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Chronic lymphocytic leukaemia (CLL) is an indolent lymphoproliferative disorder manifested by low growth fraction and prolonged survival of the malignant cells. The mechanisms that enable CLL cells to live longer and to resist apoptosis remain unclear. Because the malignant CLL cells express CD40 and Fas receptors, which can transduce cell-survival and cell-death signals, we examined the role of CD40 in the growth regulation of CLL cells and its interaction with Fas-mediated and fludarabine-induced apoptosis in vitro. Primary CLL cells underwent spontaneous apoptosis in culture, which was enhanced by exogenous human Fas ligand (FasL) or fludarabine. Exogenous CD40L rescued CLL cells from spontaneous apoptosis in a dose-dependent manner, and caused CLL cells to resist apoptosis induced by FasL or fludarabine. Patients' autologous plasma rescued CLL cells from spontaneous apoptosis, an effect that could be reversed with anti-CD40 ligand (CD40L) antibodies. The levels of soluble CD40 ligand in the sera of 51 CLL patients and 55 healthy donors were determined by enzyme-linked immunosorbent assay. The mean soluble CD40L level in normal donors was 0.29 ng/ml compared to a mean value of 0.80 ng/ml in CLL patients ($P < 0.001$). CD40L up-regulated bcl-X(L) mRNA but not bcl-2 in CLL cells within 3-6 h in culture. Our results demonstrated that serum of patients with CLL contained elevated levels of biologically active soluble CD40L, and that CD40L can prolong survival of CLL cells and mediate their resistance to FasL and fludarabine in vitro.

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